

Novel Sesquiterpenoids from the Roots of *Phyllanthus emblica*

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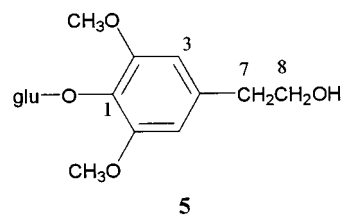
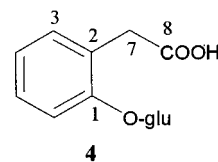
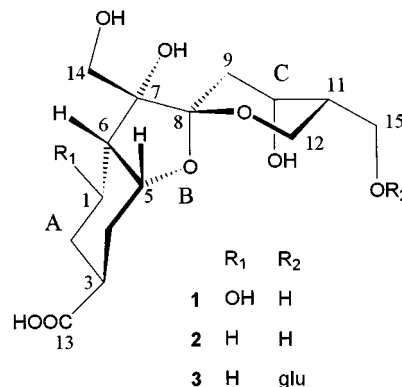
Three novel bisabolane-type sesquiterpenoids, phyllaemblic acids B (**1**) and C (**2**) and phyllaemblicin D (**3**), together with two new phenolic glycosides, 2-carboxymethylphenol 1-*O*- β -D-glucopyranoside (**4**) and 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*- β -D-glucopyranoside (**5**), were isolated from the roots of *Phyllanthus emblica*. The structures of **1**–**5** were established by spectral and chemical methods. The absolute stereochemistry of **1** and **2** was determined by applying the PGME method.

Phyllanthus emblica L. (Euphorbiaceae) is a shrub or tree found in subtropical and tropical parts of the People's Republic of China, India, Indonesia, and the Malay Peninsula. The fruit of this plant has been used widely for its antiinflammatory and antipyretic effects by local people of its growing areas. Some people living in the Southwest of China use the roots of *P. emblica* for the treatment of eczema, and in Nepal it is used as an astringent and hemostatic agent.¹ We recently reported the isolation and structure of a highly oxygenated norbisabolane, phyllaemblic acid, and its ester glycosides, phyllaemblicins A–C, from the EtOAc layer of the 60% aqueous acetone extract of the roots of this plant.^{2,3} Further investigation on the same extract has resulted in the isolation of three novel sesquiterpenoids, phyllaemblic acids B (**1**) and C (**2**) and a glucoside of **2**, phyllaemblicin D (**3**), from the BuOH layer, together with two new phenolic glycosides, 2-carboxymethylphenol 1-*O*- β -D-glucopyranoside (**4**) and 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*- β -D-glucopyranoside (**5**). This paper deals with the isolation and structure elucidation of these compounds.

Results and Discussion

A 60% aqueous acetone extract of the air-dried roots of *P. emblica* was suspended in H₂O and partitioned successively with EtOAc and 1-BuOH. The 1-BuOH layer was subjected to chromatography over Sephadex LH-20, MCI-gel CHP 20P, Chromatorex ODS, Toyopearl HW-40F, and silica gel to afford compounds **1**–**5**. Phyllaemblic acid and phyllaemblicin C, which have been previously isolated from the EtOAc layer,^{2,3} were also obtained together with three known compounds identified as 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose,⁴ 6-*O*-galloyl-D-glucose,⁵ and 1,3,5-trihydroxybenzene 1-*O*- β -D-glucoside (phlorin).⁶

Compound **1** was obtained as an off-white amorphous powder. Its molecular formula was assigned as C₁₅H₂₄O₉ on the basis of the ¹³C NMR data, the negative-ion FABMS (*m/z* 347, [M – H][–]), and elemental analysis. The ¹³C NMR spectrum of **1** showed 15 carbon resonances (Table 1) including nine oxygen-bearing carbons of three methylenes, three methines, two quaternary carbons, and a carboxyl carbon, suggesting that **1** was a highly oxygenated sesquiterpenoid. From the ¹H–¹H COSY and HMQC spectra, two partial structures of C-1 to C-6 (A ring) and C-9 to C-12, C-15 (C ring) could be deduced. HMBC correlations of C-13 with H-2, H-3, and H-4 suggested that the carboxyl carbon



(C-13) was attached to C-3. The location of the remaining three carbons, an isolated methylene [C-14, δ_C 65.9, δ_H 3.64, 3.68 (each d, 11.5)] and two quaternary carbons [δ 85.5 (C-7), and δ 108.6 (C-8)], was also straightforward from the HMBC spectrum, which showed the long-range correlations of H-1, H-5, H-6, H-14 with C-7; H-6, H-9, H-10, H-12, H-14 with C-8; and H-14 with C-6. The HMBC correlations (Figure 1, Supporting Information) confirmed that **1** was a bisabolane-type sesquiterpenoid.

The proton-coupling constants (Table 2) indicated that H-5 and H-10 were oriented equatorially, while H-1, H-3, H-6, and H-11 were oriented axially. In the NOESY spectrum of **1** (Figure 1, Supporting Information), a cross-peak between H-5 and H-12 confirmed the relative configuration of the C-8 spiro-acetal carbon, and other NOE correlations of H-5 with H-6 and H-14, and H-6 with H-14, revealed the relative configurations of C-5 to C-7 as shown.

The absolute configuration of **1** was determined by applying the phenylglycine methyl ester (PGME) method for the C-13 carboxyl group.⁷ Treatment of two aliquots of

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Table 1. ^{13}C NMR Data of Compounds **1**–**3**^a

no.	1	2	3
1	66.7	21.5	21.5
2	34.8	26.9	26.9
3	37.4	38.3	38.3
4	29.9	30.7	30.6
5	75.8	75.3	75.3
6	53.0	43.9	43.9
7	85.5	85.6	85.6
8	108.6	108.9	108.8
9	36.4	37.6	37.4
10	66.3	66.6	66.2
11	43.3	43.4	41.1
12	59.6	59.8	59.5
13	179.7	180.2	180.1
14	65.9	65.7	65.7
15	62.0	62.1	69.2
glu-1			104.3
2			75.1
3			78.0
4			71.6
5			77.9
6			62.7

^a The δ values are in ppm, data recorded in CD_3OD at 125 MHz.

1 in dimethyl formamide (DMF) with (*S*- and (*R*)-PGME in the presence of benzotriazoloxyltri(pyrrrolidinyl)phosphonium hexafluorophosphate (PyBOP), 1-hydroxybenzotriazole (HOBT), and *N*-methylmorpholine provided the corresponding PGME amides **1a** and **1b**, respectively. According to the PGME method for carboxylic acid, the $\Delta\delta(S-R)$ values (Figure 1) are assigned the *S* configuration at C-3 of **1**. On the basis of the above evidence, the absolute configuration of phyllaemblic acid B (**1**) was concluded to be as shown.

Compound **2** was obtained as an off-white amorphous powder. Comparison of the ^1H and ^{13}C NMR spectral data (Tables 1, 2) with those of **1** showed that the structure of **2** was analogous to that of **1** except for the loss of a hydroxy group at C-1, which caused the large upfield shift of C-1 to δ 21.5 (δ 66.7 in **1**) along with upfield shifts of C-2 (-7.9 ppm) and C-6 (-9.1 ppm). The lack of an oxygen atom at C-1 was also apparent from the negative-ion FABMS (m/z 331, $[\text{M} - \text{H}]^-$) and elemental analysis. The 2D NMR experiments, including $^1\text{H}-^1\text{H}$ COSY, HSQC, and HMBC (Figure 2, Supporting Information), further confirmed the structure of **2**. The NOE correlations (Figure 2, Supporting Information) together with the proton-coupling constants listed in Table 2 revealed that the relative configuration of **2** was also similar to that of **1**.

The absolute configuration of **2** was also determined by applying the PGME method. The $\Delta\delta(S-R)$ values of (*S*)-(**2a**) and (*R*)-(**2b**) PGME amides (Figure 2) led to the assignment of the *S* configuration at C-3 of **2**. Therefore, the absolute configuration of phyllaemblic acid C was established as shown in **2**.

The ^1H and ^{13}C NMR spectral data of compound **3** (Tables 1 and 2) were similar to those of **2**, except for a downfield shift of C-15 ($+7.1$ ppm) and an upfield shift of C-11 (-2.3 ppm) and the appearance of a set of signals due to a hexose moiety, suggesting that **3** was the 15-*O*-glucoside of **2**. The sugar moiety was determined to be β -D-glucopyranose on the basis of its large coupling constants of the pyranose ring protons ($J_{1,2} = 7.5$ Hz, $J_{2,3} = J_{3,4} = J_{4,5} = 8.5$ Hz) (Table 2). The location of the sugar moiety was further confirmed by the long-range correlations between the anomeric proton (δ 4.27) of the glucose and C-15 (δ 69.2) in the HMBC spectrum. On the basis of the above evidence, the structure of phyllaemblicin D (**3**) was established as shown.

Compound **4** was obtained as a tan amorphous powder and showed the $[\text{M} - \text{H}]^-$ peak at m/z 313 in the negative-ion FABMS spectrum. The ^{13}C NMR spectrum of **4** showed 14 carbon resonances including a benzene ring, a set of signals due to a hexose moiety, a benzylic methylene (δ 38.0), and a carboxyl group (δ 177.6). The benzene ring was suggested to be *ortho*-substituted on the basis of the coupling pattern of the aromatic protons in the ^1H NMR spectrum, which showed four aromatic proton signals at δ 7.01 (1H, br t, $J = 7.5$, H-4), 7.19 (1H, br t, $J = 7.5$, H-5), 7.48 (1H, br d, $J = 7.5$ Hz, H-6), and 7.56 (1H, br d, $J = 7.5$ Hz, H-3) in pyridine-*d*₅. The chemical shift (δ 157.2) of one of the aromatic carbons indicated that it was attached to an oxygen atom, and the chemical shift of the sugar anomeric proton [δ_{H} 4.87 (d, $J = 7.5$ Hz)] and carbon (δ 103.2) signals indicated that the sugar moiety was not attached to the carboxyl group but to this phenolic oxygen through a glycosidic linkage. Owing to the overlapping of the proton signals, the sugar moiety could not be determined directly by ^1H NMR analysis of **4**; however, it was easily confirmed to be β -D-glucopyranose by complete assignments of the sugar proton signals of the peracetate **4a** ($J_{1,2} = 7.5$ Hz, $J_{2,3} = J_{3,4} = J_{4,5} = 9.0$ Hz). According to the above evidence, the structure of **4** was characterized as 2-carboxylmethylphenol 1-*O*- β -D-glucopyranoside.

Compound **5** had the molecular formula $\text{C}_{16}\text{H}_{24}\text{O}_9$ on the basis of the ^{13}C NMR data, the positive-ion FABMS (m/z 383, $[\text{M} + \text{Na}]^+$), and elemental analysis. The ^{13}C NMR spectrum of **5** showed four signals due to a benzene ring, two methoxyl signals at δ 57.0, and two methylene signals at δ 40.4 and 64.1, along with a set of signals rising from a hexose moiety, which was determined to be β -D-glucopyranose based on its large proton-coupling constants. The ^1H NMR spectrum of **5** exhibited a two-proton aromatic singlet at δ 6.58 (s) and a singlet at δ 3.84 due to two methoxyl groups, suggesting the existence of a 1,2,4,6-tetrasubstituted symmetric benzene ring. In the HMBC spectra (Figure 3, Supporting Information) of **5**, an oxygen-bearing aromatic carbon [δ 134.8 (C-1)] was correlated with both the sugar anomeric proton and the aromatic methine protons, and the aromatic methine carbons [δ 108.0 (C-3, 5)] were coupled with the benzylic methylene proton (δ 2.77). This observation revealed that the glucose moiety was attached to C-1 and the 2-hydroxyethyl group was attached to C-4. Therefore, the structure of **5** was determined to be 2,6-dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*- β -D-glucopyranoside.

Although compounds **1**–**3** were minor constituents of the root of *P. emblica*, their skeleton and the position of oxygenation were closely related to those of phyllaemblic acid and phyllaemblicin A–C, which were the major constituents with a norbisabolane skeleton.^{2,3} Related bisabolanes and norbisabolanes have been isolated from *P. acidus*⁸ and *P. acuminatus*.^{9,10} Compounds **1**–**3** possess an aglycon similar to that of the potent antineoplastic phyllanthostatins 1–6, the bisabolane glycosides with acetyl groups isolated from *P. acuminatus* by Pettit and co-workers.^{9,10} However, our previous work showed no cytotoxic activity for phyllaemblic acid and phyllaemblicin A,³ and the desacetyl derivatives of phyllanthostatin were also found to be inactive against the PS cell line.¹¹

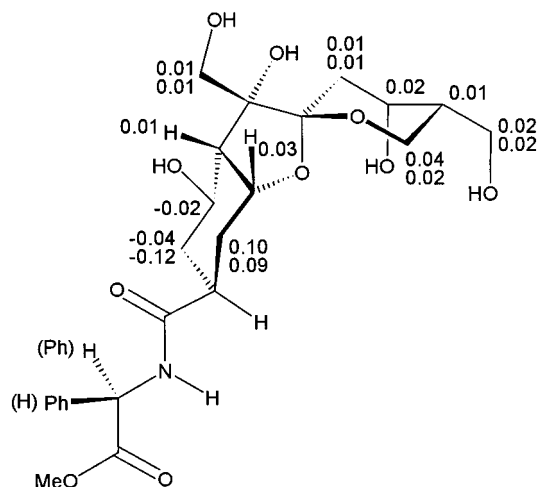
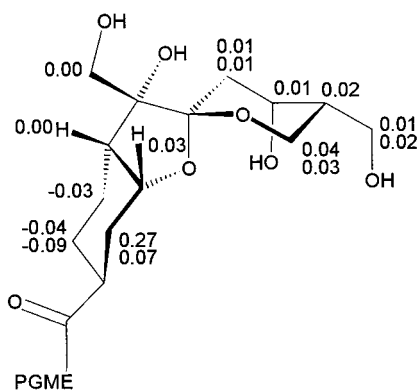
Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in CD_3OD , pyridine-*d*₅, and C_6D_6 with Varian Unity plus 500 and Varian Gemini 300 spectrometers operating at 500 and 300 MHz for ^1H and

Table 2. ^1H NMR Data of Compounds 1–3^a

no.	1	2	3
H-1	4.00 (ddd, 4.0, 9.0, 12.0)	1.59 (m)	1.59 (m)
2	1.49 (q, 12.0)	1.42 (ddt, 5.0, 10.5, 11.5)	1.42 (m)
	2.15 (ddd, 4.0, 6.0, 12.0)	1.99 (m, overlapped)	2.00 (m, overlapped)
3	2.75 (ddt, 6.0, 7.0, 12.0)	2.61 (dddd, 5.0, 5.5, 10.0, 10.5)	2.62 (dddd, 5.0, 5.0, 10.0, 10.0)
4	1.98 (dt, 7.0, 14.0)	1.88 (ddd, 5.0, 10.0, 14.0)	1.88 (ddd, 5.0, 10.0, 13.5)
	1.92 (m, overlapped)	2.07 (ddd, 5.5, 6.5, 14.0)	2.08 (m)
5	4.28 (dt, 5.0, 7.0)	4.22 (q, 5.5)	4.22 (q, 5.5)
6	2.07 (dd, 7.0, 9.0)	2.10 (dt, 10.0, 5.5)	2.10 (m)
9	2.06 (dd, 4.0, 14.0)	2.02 (dd, 3.0, 14.5)	2.03 (dd, 3.0, 15.0)
	1.92 (dd, 3.0, 14.0)	1.96 (dd, 3.0, 14.5)	1.97 (dd, 3.0, 15.0)
10	4.07 (br d, 2.5)	4.06 (br d, 3.0)	4.11 (br d, 2.5)
11	1.87 (m)	2.07 (m, overlapped)	2.09 (m)
12	3.81 (t, 11.5)	3.84 (t, 11.5)	3.83 (t, 11.5)
	3.64 (dd, 7.0, 11.5)	3.65 (dd, 5.0, 11.5)	3.65 (dd, 6.5, 11.5)
14	3.68 (d, 11.5)	3.69 (d, 12.0)	3.69 (d, 11.5)
	3.64 (d, 11.5)	3.57 (d, 12.0)	3.57 (d, 11.5)
15	3.60 (dd, 6.0, 11.0)	3.61 (dd, 6.5, 11.0)	3.61 (dd, 7.0, 10.0)
	3.46 (dd, 7.5, 11.0)	3.47 (dd, 7.0, 11.0)	3.77 (dd, 7.5, 10.0)
glu-1			4.27 (d, 7.5)
2			3.17 (dd, 7.5, 8.5)
3			3.36 (t, 8.5)
4			3.28 (t, 8.5)
5			3.27 (ddd, 2.5, 5.0, 8.5)
6			3.86 (dd, 2.5, 12.0)
			3.67 (dd, 5.0, 12.0)

^a The δ values are in ppm, data recorded in CD_3OD at 500 MHz.

**Figure 1.** $\Delta\delta(S-R)$ values (in ppm) for PGME amide derivatives of 1.**Figure 2.** $\Delta\delta(S-R)$ values (in ppm) for PGME amide derivatives of 2.

125 and 75 for ^{13}C , respectively. Coupling constants are expressed in Hz, and chemical shifts are given on a δ (ppm) scale with tetramethylsilane as the internal standard. MS were recorded on a JEOL JMS DX-303 spectrometer, and glycerol was used as a matrix for FABMS measurement. Column chromatography was performed with Kieselgel 60 (70–230 mesh,

Merck), MCI-gel CHP 20P (75–150 μm , Mitsubishi Chemical Co.), Sephadex LH-20 (25–100 μm , Pharmacia Fine Chemical Co. Ltd.), Toyopearl HW-40F (37–70 μm , Tosoh Co.), and Chromatorex ODS (100–200 mesh, Fuji Silysia Chemical Ltd.). TLC was performed on precoated Kieselgel 60 F₂₅₄ plates (0.2 mm thick, Merck), and spots were detected by ultraviolet (UV) illumination and by spraying with 10% sulfuric acid reagent.

Plant Material. The roots of *Phyllanthus emblica* L. were collected at Wenshan, Yunnan, People's Republic of China. A voucher specimen is deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried roots (8.0 kg) were extracted with 60% aqueous acetone four times at room temperature to give an extract (450 g), which was suspended in H_2O and then partitioned successively with EtOAc and 1-BuOH. After concentration in vacuo, the 1-BuOH layer (117 g) was chromatographed over Sephadex LH-20 (H_2O –MeOH, 1:0–0:1) and MCI gel CHP 20P (H_2O –MeOH, 0–60%) to give four fractions (fractions 1–4). Fraction 1 was taken forward to MCI gel CHP 20P (H_2O –MeOH, 1:0–0:1) to afford six fractions (fractions 1-1–1-6). Fraction 1-2 was applied to a column of Toyopearl HW-40F (10–60% MeOH) to give 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (21 mg) and phlorin (30 mg). Repeated chromatographies of fraction 1-3 over Chromatorex ODS (0%–40% MeOH), MCI gel CHP 20P (0–50% MeOH), silica gel (CHCl_3 –MeOH– H_2O , 9:1:0.1–5:5:1), and Toyopearl HW-40F (10%–60% MeOH) afforded compound 1 (142 mg) and 6-*O*-galloyl-D-glucose (19 mg). Purification of fraction 1-4 with Chromatorex ODS (10%–35% MeOH) and MCI gel CHP 20P (10%–40% MeOH) gave compound 3 (57 mg). Fraction 1-5 was subjected to Chromatorex ODS (10%–40% MeOH), MCI gel CHP 20P (10%–50% MeOH), and silica gel (CHCl_3 –MeOH– H_2O , 8.5:1.5:0.1–6:4:1) to afford compounds 2 (26 mg), 4 (63 mg), and 5 (11 mg). Fraction 2 was repeatedly chromatographed over MCI gel CHP 20P (H_2O –MeOH, 1:0–0:1), Chromatorex ODS (0–70% MeOH), and silica gel (CHCl_3 –MeOH– H_2O , 9:1:0.1–7:3:0.5) to yield phyllaemblic acid (50 mg) and phyllaemblicin C (1.32 g).

Phyllaemblic acid B (1): off-white amorphous powder; $[\alpha]_{\text{D}}^{17} +58.7^\circ$ (*c* 0.46, MeOH); ^1H and ^{13}C NMR data, see Tables 1 and 2; FABMS m/z 695 $[\text{2M} - \text{H}]^-$ (18), 347 $[\text{M} - \text{H}]^-$ (100); *anal.* C 49.24%, H 6.86%, calcd for $\text{C}_{15}\text{H}_{24}\text{O}_9 \cdot \text{H}_2\text{O}$, C 49.18%, H 7.15%.

Condensation of 1 with (*S*)-PGME. To a stirred solution containing a mixture of 1 (3.0 mg) and (*S*)-PGME (3.6 mg) in DMF (1.0 mL) were successively added PyBOP (6.7 mg), HOBT

(2.0 mg), and *N*-methylmorpholine (3.5 μ L) at 0 °C. After stirring at room temperature for 1.5 h, the mixture was applied to a MCI gel CH20P column, eluting with H₂O and 50% aqueous acetone. After concentrating to dryness, the 50% aqueous acetone fraction was subjected to a silica gel column (CHCl₃-MeOH-H₂O, 9:1:0.1) to afford the (*S*)-PGME amide (**1a**, 3.0 mg): ¹H NMR (CD₃OD, 500 MHz) δ 7.39–7.33 (5H, m, Ar-H), 5.44 (1H, s, NH), 4.83 (1H, s, C α -H), 4.33 (1H, ddd, *J* = 4.5, 7.0, 7.0 Hz, H-5), 4.07 (1H, br d, *J* = 3.0 Hz, H-10), 3.98 (1H, ddd, *J* = 4.0, 9.0, 12.0 Hz, H-1), 3.83 (1H, t, *J* = 11.5 Hz, H-12a), 3.67 (1H, d, *J* = 11.5 Hz, H-14a), 3.64 (1H, d, *J* = 11.5 Hz, H-14b), 3.63 (1H, dd, *J* = 8.0, 11.5 Hz, H-12b), 3.61 (1H, dd, *J* = 6.5, 11.0 Hz, H-15a), 3.47 (1H, dd, *J* = 7.5, 11.0 Hz, H-15b), 2.83 (1H, dddd, *J* = 6.5, 7.5, 11.5, 13.5 Hz, H-3), 2.06 (1H, dd, *J* = 7.0, 9.0 Hz, H-6), 2.04 (1H, dd, *J* = 2.5, 14.0 Hz, H-9a), 1.99 (1H, dd, *J* = 7.0, 14.0 Hz, H-4a), 1.95 (1H, m, H-2a), 1.92 (1H, dd, *J* = 3.5, 14.0 Hz, H-9b), 1.86 (1H, ddd, *J* = 4.5, 7.5, 14.0 Hz, H-4b), 1.86 (1H, m, H-11), 1.49 (1H, ddd, *J* = 12.0, 11.5, 12.0 Hz, H-2b).

Condensation of 1 with (*R*)-PGME. Compound **1** (3.0 mg) was condensed with (*R*)-PGME under the same conditions as above to yield (*R*)-PGME amide (**1b**, 2.8 mg): ¹H NMR (CD₃OD, 500 MHz) δ 7.39–7.33 (5H, m, Ar-H), 5.45 (1H, s, NH), 4.83 (1H, s, C α -H), 4.30 (1H, ddd, *J* = 6.5, 7.0, 4.5 Hz, H-5), 4.05 (1H, br d, *J* = 2.5 Hz, H-10), 4.00 (1H, ddd, *J* = 4.0, 9.0, 12.0 Hz, H-1), 3.79 (1H, t, *J* = 12.0 Hz, H-12a), 3.66 (1H, d, *J* = 11.5 Hz, H-14a), 3.63 (1H, d, *J* = 11.5 Hz, H-14b), 3.61 (1H, dd, *J* = 7.0, 12.0 Hz, H-12b), 3.59 (1H, dd, *J* = 6.5, 11.0 Hz, H-15a), 3.45 (1H, dd, *J* = 7.5, 11.0 Hz, H-15b), 2.83 (1H, dddd, *J* = 6.0, 7.5, 11.5, 13.5 Hz, H-3), 2.07 (1H, ddd, *J* = 4.0, 6.0, 12.0 Hz, H-2a), 2.05 (1H, dd, *J* = 7.0, 9.0 Hz, H-6), 2.03 (1H, dd, *J* = 3.0, 14.5 Hz, H-9a), 1.91 (1H, dd, *J* = 3.5, 14.5 Hz, H-9b), 1.89 (1H, dd, *J* = 6.5, 14.0 Hz, H-4a), 1.85 (1H, m, H-11), 1.77 (1H, ddd, *J* = 4.5, 7.5, 14.0 Hz, H-4b), 1.53 (1H, ddd, *J* = 11.5, 12.0, 12.0 Hz, H-2b).

Phyllaemblic acid (2): off-white amorphous powder; $[\alpha]_D^{17} + 80.6^\circ$ (*c* 0.32, MeOH); ¹H and ¹³C NMR data, see Tables 1 and 2; FABMS *m/z* 663 [2M – H][–] (18), 331 [M – H][–] (50); *anal.* C 51.23%, H 7.02%, calcd for C₁₅H₂₄O₈·H₂O, C 51.42%, H 7.48%.

Condensation of 2 with (*S*)-PGME. To a stirred solution containing a mixture of **2** (3.0 mg) and (*S*)-PGME (3.6 mg) in DMF (1.0 mL) were successively added PyBOP (6.7 mg), HOBT (2.0 mg), and *N*-methylmorpholine (3.5 μ L) at 0 °C. After stirring at room temperature for 1.5 h, the mixture was applied to a MCI gel CH20P column, eluting with H₂O and 50% aqueous acetone; this fraction was then subjected to a silica gel column (CHCl₃-MeOH-H₂O, 9:1:0.1) to afford the (*S*)-PGME amide (1.8 mg): ¹H NMR (CD₃OD, 500 MHz) δ 7.38–7.33 (5H, m, Ar-H), 5.44 (1H, s, NH), 4.84 (1H, s, C α -H), 4.24 (1H, q, *J* = 5.0 Hz, H-5), 4.06 (1H, br d, *J* = 3.0 Hz, H-10), 3.87 (1H, t, *J* = 12.0 Hz, H-12a), 3.68 (1H, d, *J* = 11.5 Hz, H-14a), 3.65 (1H, dd, *J* = 5.0, 12.0 Hz, H-12b), 3.62 (1H, dd, *J* = 6.0, 11.0 Hz, H-15a), 3.56 (1H, d, *J* = 11.5 Hz, H-14b), 3.47 (1H, dd, *J* = 7.5, 11.0 Hz, H-15b), 2.68 (1H, m, H-3), 2.08 (1H, m, H-4a), 2.07 (1H, m, H-6), 2.00 (1H, dd, *J* = 3.0, 15.0 Hz, H-9a), 1.95 (1H, dd, *J* = 3.0, 15.0 Hz, H-9b), 1.88 (1H, m, H-11), 1.84 (1H, ddd, *J* = 4.0, 10.0, 14.0 Hz, H-4b), 1.80 (1H, m, H-2a), 1.57 (2H, m, H-1), 1.40 (1H, tdd, *J* = 4.0, 12.0, 12.0 Hz, H-2b).

Condensation of 2 with (*R*)-PGME. Compound **2** (3.0 mg) was condensed with (*R*)-PGME under the same conditions as above to yield (*R*)-PGME amide (1.7 mg): ¹H NMR (CD₃OD, 500 MHz) δ 7.38–7.33 (5H, m, Ar-H), 5.44 (1H, s, NH), 4.84 (1H, s, C α -H), 4.21 (1H, q, *J* = 5.0 Hz, H-5), 4.05 (1H, br d, *J* = 3.0 Hz, H-10), 3.83 (1H, t, *J* = 11.5 Hz, H-12a), 3.68 (1H, d, *J* = 11.5 Hz, H-14a), 3.62 (1H, dd, *J* = 4.0, 11.5 Hz, H-12b), 3.60 (1H, dd, *J* = 4.5, 11.0 Hz, H-15a), 3.56 (1H, d, *J* = 11.5 Hz, H-14b), 3.45 (1H, dd, *J* = 7.5, 11.0 Hz, H-15b), 2.68 (1H, m, H-3), 2.07 (1H, ddd, *J* = 6.0, 6.0, 12.0 Hz, H-6), 1.99 (1H, dd, *J* = 3.0, 15.0 Hz, H-9a), 1.94 (1H, dd, *J* = 3.0, 15.0 Hz, H-9b), 1.89 (1H, m, H-2a), 1.86 (1H, m, H-11), 1.81 (1H, m, H-4a), 1.77 (1H, ddd, *J* = 4.5, 10.0, 14.0 Hz, H-4b), 1.60 (2H, m, H-1), 1.44 (1H, tdd, *J* = 4.0, 12.0, 12.0 Hz, H-2b).

Phyllaemblicin D (3): off-white amorphous powder; $[\alpha]_D^{17} + 32.5^\circ$ (*c* 0.31, MeOH); ¹H and ¹³C NMR data, see Tables 1

and 2; FABMS *m/z* 493 [M – H][–] (100); *anal.* C 48.01%, H 6.70%, calcd for C₂₁H₃₄O₁₃·3/2H₂O, C 48.36%, H 7.15%.

2-Carboxylmethylphenol 1-*O*- β -D-glucopyranoside (4): tan amorphous powder; $[\alpha]_D^{20} - 30.5^\circ$ (*c* 0.7, MeOH); ¹H NMR (CD₃OD, 500 MHz) δ 7.22–7.16 (3H, m, H-3,5,6), 6.98 (1H, td, *J* = 7.5, 1.5 Hz, H-4), 4.87 (1H, d, *J* = 7.0 Hz, glc H-1'), 3.88 (1H, dd, *J* = 1.5, 12.0 Hz, H-6'a), 3.70 (1H, dd, *J* = 5.0, 12.0 Hz, H-6'b), 3.67 (1H, d, *J* = 15.0 Hz, H-7a), 3.62 (1H, d, *J* = 15.0 Hz, H-7b), 3.52–3.37 (4H, m, H-2', 3', 4', 5'); ¹H NMR (C₆D₅N, 300 MHz) δ 7.56 (1H, br d, *J* = 7.5 Hz, H-3), 7.48 (1H, br d, *J* = 7.5 Hz, H-6), 7.19 (1H, br t, *J* = 7.5, H-7), 7.01 (1H, br t, *J* = 7.5, H-4), 5.48 (1H, br s, glc H-1'), 4.50 (1H, br d, *J* = 1.5, 12.0 Hz, H-6'a), 4.37 (1H, dd, *J* = 4.8, 12.0 Hz, H-6'b), 4.04, 4.10, 4.30 (6H, each br s, H-7, 2', 3', 4', 5'); ¹³C NMR (CD₃OD, 75 MHz) δ 177.6 (C-8), 157.2 (C-1), 132.1 (C-3), 129.5 (C-5), 126.8 (C-2), 123.5 (C-4), 116.6 (C-6), 103.2 (glc C-1'), 78.1, 77.7 (C-3', 5'), 74.9 (C-2'), 71.3 (C-4'), 62.5 (C-6'), 38.0 (C-7); FABMS *m/z* 313 [M – H][–] (100); *anal.* C 50.04%, H 5.65%, calcd for C₁₄H₁₈O₈·5/4H₂O, C 49.92%, H 6.13%.

Acetylation of 4. Compound **4** (10 mg) was treated with pyridine (1 mL) and acetic anhydride (1 mL) at room temperature for 6 h. The reaction mixture was poured into ice-water, and the resulting white precipitate was collected by filtration. The precipitate was then purified by chromatography over silica gel with CHCl₃-MeOH (96:4) to give peracetate **4a** (3 mg): ¹H NMR (C₆D₆, 300 MHz) δ 7.06–6.93 (3H, m, H-3, 5, 6), 6.83 (1H, br t, *J* = 7.2, H-4), 5.48 (1H, dd, *J* = 7.5, 9.0 Hz, H-4'), 5.39 (1H, t, *J* = 9.0 Hz, H-3'), 5.26 (1H, t, *J* = 9.0 Hz, H-4'), 4.82 (1H, d, *J* = 7.5 Hz, H-1'), 4.15 (1H, br d, *J* = 4.8, 12.3 Hz, H-6'a), 3.96 (1H, dd, *J* = 2.1, 12.3 Hz, H-6'b), 3.63 (1H, d, *J* = 16.8 Hz, H-7a), 3.37 (1H, d, *J* = 16.8 Hz, H-7b), 3.18 (1H, ddd, *J* = 2.0, 4.8, 9.0 Hz, H-5'), 1.82, 1.72, 1.67, 1.64 (each 3H, s, OCOCH₃).

2,6-Dimethoxy-4-(2-hydroxyethyl)phenol 1-*O*- β -D-glucopyranoside (5): off-white amorphous powder; $[\alpha]_D^{20} + 19.3^\circ$ (*c* 0.7, MeOH); ¹H NMR (CD₃OD, 500 MHz) δ 6.58 (2H, s, H-3, 5), 4.80 (1H, d, *J* = 7.5 Hz, glc H-1'), 3.84 (6H, s, –OCH₃), 3.77 (1H, dd, *J* = 2.5, 12.0 Hz, H-6'a), 3.75 (2H, t, *J* = 6.5 Hz, H-8), 3.66 (1H, dd, *J* = 5.5, 12.0 Hz, H-6'b), 3.47 (1H, dd, *J* = 7.5, 9.5 Hz, H-2'), 3.40 (2H, m, H-3', 4'), 3.19 (1H, ddd, *J* = 2.5, 5.5, 9.5 Hz, H-5'), 2.77 (1H, t, *J* = 6.5 Hz, H-7); ¹³C NMR (CD₃OD, 125 MHz) δ 154.1 (C-2, 6), 137.4 (C-4), 134.8 (C-1), 108.0 (C-3, 5), 105.6 (glc C-1'), 78.3 (C-5'), 77.8 (C-3'), 75.7 (C-2'), 71.3 (C-4'), 64.1 (C-8), 62.6 (C-6'), 57.0 (–OCH₃), 40.4 (C-7); FABMS *m/z* 383 [M + Na]⁺ (70), 198 (68); *anal.* C 52.61%, H 6.69%, calcd for C₁₆H₂₄O₉·1/4H₂O, C 52.67%, H 6.77%.

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Supporting Information Available: Selective HMBC and NOESY correlations of compounds **1**, **2**, and **5** (Figures 1–3). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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